Surgical Debulking of Ovarian Cancer: What Difference Does It Make?

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Three-quarters of women who are newly diagnosed with invasive epithelial ovarian cancer present with stage III to IV disease. Recent data on the efficacy of neoadjuvant chemotherapy have served to challenge the conventional dogma that the preferred initial treatment is surgical debulking. Most of these patients will achieve remission regardless of initial treatment, but 80% to 90% of patients will ultimately relapse. The timing and clinical benefit of a second debulking operation is even more contentious. This article focuses on the recent debate of when or if patients with ovarian cancer should undergo aggressive surgical resection of bulky disease.
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Key words: Ovarian cancer • Primary debulking surgery • Neoadjuvant chemotherapy • Interval debulking surgery • Secondary debulking surgery

Worldwide, approximately 200,000 women are diagnosed with ovarian cancer and 125,000 die each year.[1] Although cervical cancer accounts for 275,000 global annual deaths, ovarian cancer mortality exceeds the combined total of all other gynecologic malignancies in the United States. Currently, it is the ninth leading cause of cancer in women, but the fifth leading cause of all cancer-related deaths. In 2009, 21,550 new cases and 14,600 deaths were estimated.[2] One in 78 American women (1.3%) will be diagnosed with this highly lethal disease during their lifetime.

Table 1
Symptoms of Ovarian Cancer

Bloating
Pelvic or abdominal pain
Difficulty eating or feeling full quickly
Frequent urination

Ovarian cancer is often portrayed as the disease that whispers because it does not present with dramatic bleeding, excruciating pain, or an obvious lump. Instead, the typical symptoms tend to be indolent (Table 1). Patients and their health care providers often attribute such nonspecific changes to menopause, aging, dietary indiscretions, stress, depression, or functional bowel problems. Frequently, women are medically managed for indigestion or other presumed ailments without having a pelvic examination.[3] As a result, substantial delays prior to diagnosis are very common.

Unfortunately, there is no effective screening test. Routinely checking serum cancer antigen 125 (CA 125) markers or transvaginal sonograms do not result in early detection or reduced mortality in either the general or high-risk populations. Currently, there is no recommendation for routine ovarian cancer screening from any national organization.[4] Despite enormous efforts at patient education and because of the expense of screening trials, minimal progress has been achieved to reliably detect ovarian cancer at a more curable stage. Three-quarters of women still present, as they always have, with advanced disease typically characterized by ascites, carcinomatosis, and omental caking (Figure 1).

Fewer than half of such patients will be cared for by a gynecologic oncologist.[5,6] Physicians not familiar with the expected, often dramatic, response of ovarian cancer to aggressive treatment may discover extensive carcinomatosis and assume that death is imminent. For example, a consulting general surgeon may perform a diverting colostomy for obstructive symptoms and the patient afterward might be treated with palliative chemotherapy or, worse, be directed to hospice. When a gynecologic oncologist is involved, survival is demonstrably improved. Patients are more likely to undergo a comprehensive debulking procedure and receive postoperative chemotherapy.[7,8]

Removal of bulky tumors as part of cancer treatment is an easy concept for patients and their families to understand. When ovarian cancer is initially suspected, they usually expect an operation and are often greatly relieved when their surgeon proudly states that "more than 90% of the tumor was removed" at the time of surgery. In theory, fewer cancer cells at the start of chemotherapy should lead to a higher likelihood of cure. However, by the time advanced ovarian cancers are diagnosed, approximately 10^{10} to 10^{11} malignant cells are present. Optimal debulking of 90% of the aggregate tumor represents 1 log cell kill. In contrast, a single course of chemotherapy may produce up to a 2 to 3 log cell kill, representing a 99.0% to 99.9% reduction in tumor cells.

As most ovarian cancers demonstrate a comparable level of chemosensitivity to platinum-based chemotherapy, the actual clinical benefits of debulking have been harder to prove. Several supportive, but mostly theoretical, additional arguments have been proposed to justify the biologic plausibility of debulking (Table 2).[9,10] However, within the broader field of oncology, the aggressive surgical approach to ovarian cancer is unique. No other malignancies have shown demonstrable advantages in the setting of disseminated disease.

About one-quarter of patients have tumors where the amount of

Figure 1. *Omental caking.*

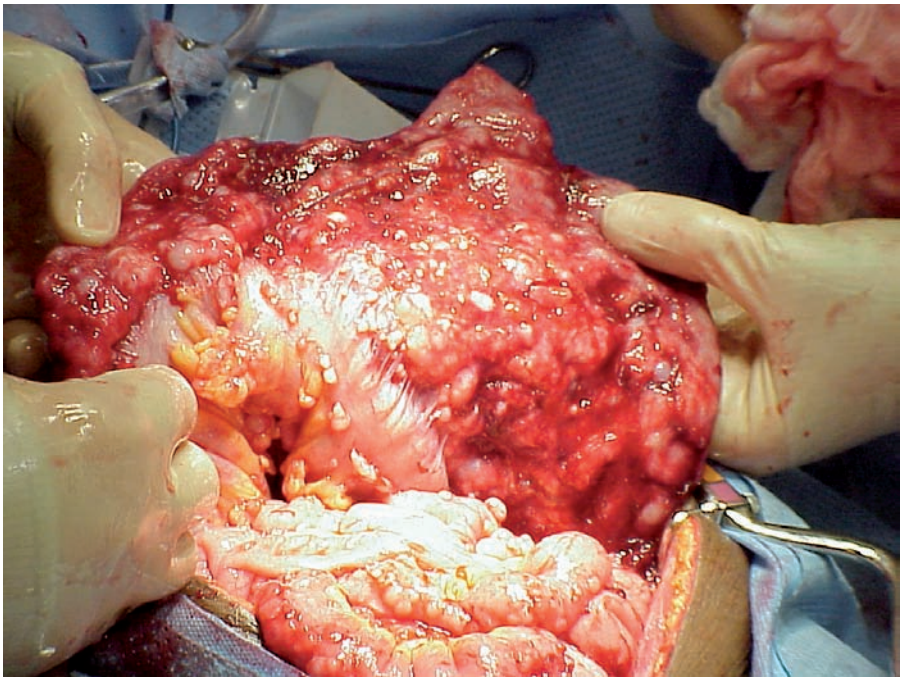


Table 2
Theoretical Arguments for Debulking Surgery

- Removing large necrotic masses promotes drug delivery to smaller tumors with good blood supply
- Removing resistant clones decreases the likelihood of early onset drug resistance
- Tiny implants have a higher growth fraction that should be more chemosensitive
- Removing cancer in specific locations, such as tumors causing a bowel obstruction, improves the patient's nutritional and immunologic status

chemotherapeutic cell kill is significantly less. For these platinum-resistant or -refractory tumors, the prognosis is uniformly poor and there are few data to support aggressive treatment. During debulking surgery and afterward, morbidity may be substantial. Overall, the majority of women will eventually succumb to their disease within a few years and thus it is important to critically evaluate both quality and length of life.

Recent innovations in chemotherapeutic drugs and their administration (ie, intraperitoneal delivery) have largely eclipsed advances in surgery. In the future, biologic agents and those drugs specifically targeting aberrant molecular pathways offer great promise for the medical management of ovarian cancer. This article focuses on the recent debate of when or if patients with ovarian cancer should undergo surgical debulking.

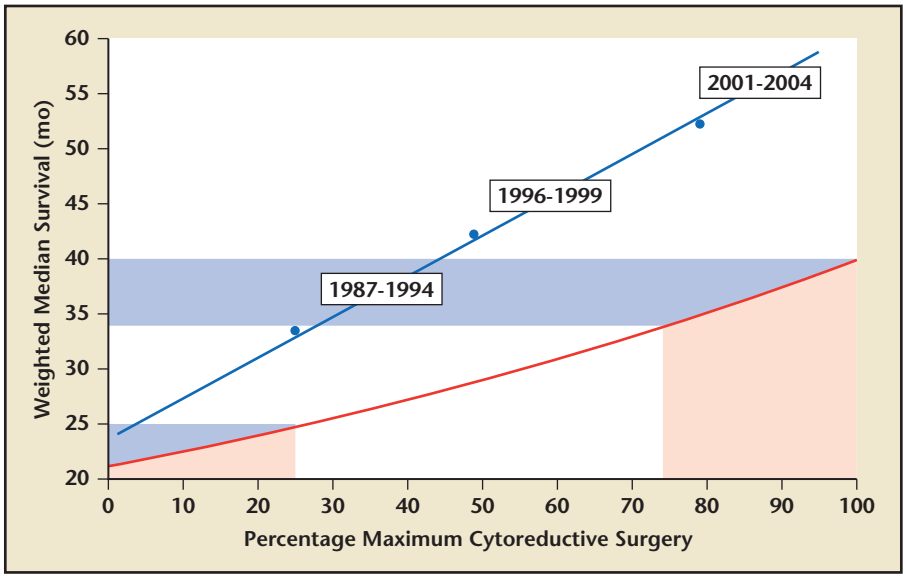
Primary Debulking Surgery

Dr. Joe V. Meigs, a gynecologic surgeon at Massachusetts General Hospital, in Boston, initially described ovarian tumor debulking in 1934.[11] However, the concept did not catch on until the mid-1970s when Dr. C. Thomas Griffiths published his seminal paper.[12] Case series and other retrospective data rapidly accrued thereafter to further support the efficacy of this approach.[13-18] For the past 3 decades, it has largely been conventional dogma that the preferred initial treatment of women with advanced ovarian cancer is surgical debulking.

The success of the operation depends on numerous factors, including patient selection, the locations of tumors, and surgeon expertise. To achieve a survival benefit, the surgery should result in no residual tumors individually measuring more than 2 cm in size.[19] For purposes of uniformity, the Gynecologic Oncology Group (GOG) has defined optimal debulking as residual implants less than 1 cm.[20] Such measurements are subjectively determined at the completion of surgery. Due to tissue induration or inadequate exploration, assessments of residual tumor size are often not entirely accurate.[21] Regardless, the penultimate goal is to achieve complete resection with no visible or palpable remaining disease anywhere in the abdomen.

Despite the accumulated evidence supporting the importance of debulking, it remains controversial whether the better outcome is due to the surgeon's technical proficiency or the intrinsic biology of the cancer that makes the tumors easier to remove.[22,23] Extensive upper abdominal disease is generally considered indicative of aggressive tumor biology. Although this is often a location of unresectable disease, optimal debulking may still be achieved in many patients by performing ultraradical procedures, such as splenectomy or diaphragmatic resection.[24,25] Survival rates have been shown to improve accordingly when the surgical paradigm is revised to a more aggressive philosophy incorporating these and other radical techniques (Figure 2).[26,27] Patients referred to specialized centers where such radical procedures are

Figure 2. *Survival effect of maximal cytoreductive surgery. Reprinted from* Gynecologic Oncology, *Vol. 114, Chi DS et al, "Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm," pp. 26-31, Copyright 2009, with permission from Elsevier.*[26]



commonly performed more often achieve a complete resection and improved survival.[28]

Suboptimal Surgical Attempt: Interval Debulking Surgery

For the most part, upfront surgery is only beneficial in those patients who can be optimally debulked. Unfortunately, preoperative CA 125 levels, computed tomography (CT) scans, and physical examinations are often not reliable to predict the intraoperative findings.[29] As a result, many patients taken to the operating room will be left with significant amounts of residual disease. Whether patients are optimally debulked, the postoperative recovery may be prolonged and fraught with complications. Not infrequently the initiation of chemotherapy is delayed or postponed indefinitely.

Neoadjuvant Chemotherapy With Interval Debulking Surgery

Some patients are too medically ill to initially undergo any type of abdominal operation, whereas others have disease that is obviously too extensive to be resected by an experienced ovarian cancer surgical team. In these circumstances, neoadjuvant chemotherapy (NACT) is routinely used, usually after the diagnosis has been confirmed by paracentesis or CT-guided biopsy. Following a few courses of treatment, the feasibility of surgery can be reassessed. In some series, NACT followed by interval debulking demonstrated comparable survival outcomes to those reported for primary surgery.[33] In addition, fewer radical procedures were required, the rate of achieving minimal residual disease was higher, and patients experienced less morbidity.[34-36] However, other reports have suggested that NACT in lieu of primary debulking is associated with an inferior overall survival.[37] Direct comparisons have been difficult to perform.

Interval debulking appears to yield benefit only among the patients whose primary surgery was not performed by a gynecologic oncologist, if the first try was not intended as a maximal resection of all gross disease, or if no upfront surgery was performed at all.

Two phase III trials were conducted to determine whether a second interval debulking procedure was worthwhile after an unsuccessful initial attempt followed by a few courses of chemotherapy. The European Organization for Research and Treatment of Cancer (EORTC) trial demonstrated a 6-month median survival advantage in patients who were re-explored after 3 cycles of chemotherapy.[30] In contrast, no survival advantage was demonstrated when a similar study was conducted through the GOG.[31] These conflicting reports are most easily explained by clarifying who performed the first surgery.

In the GOG trial, virtually all patients had their initial attempt by a gynecologic oncologist, unlike the European study where relatively few had their first surgery performed by a subspecialist. Thus, interval debulking appears to yield benefit only among the patients whose primary surgery was not performed by a gynecologic oncologist, if the first try was not intended as a maximal resection of all gross disease, or if no upfront surgery was performed at all.[32]

In 1986, the GOG and a collaborative group in the Netherlands separately opened randomized phase III trials to test the hypothesis that primary debulking was superior to NACT in advanced ovarian cancer. Both studies were closed due to poor accrual. One prevailing opinion is that clinicians did not want to subject their patients to substandard NACT treatment. Until recently, the benefits of primary surgical cytoreduction in ovarian cancer had not been rigorously tested.

The results of a randomized phase III trial conducted by the EORTC were first presented in October 2008. Although the manuscript has yet to be published, the data have reignited the debate of how best to initially treat women with advanced ovarian cancer. In the study, 704 patients were randomized to primary debulking surgery versus NACT. After 3 courses of platinum-based treatment, NACT patients who demonstrated a response underwent interval debulking. The authors reported a median overall survival that was about 30 months, regardless of assigned treatment group. In the multivariate analysis, optimal debulking was identified as the strongest independent prognostic factor, but the timing of surgery did not seem to matter. Based on the authors' interpretation of their data, NACT and interval debulking was the preferred treatment due to the lower morbidity.

At least 2 valid criticisms of the EORTC trial have been alleged. First, the duration of patient survival in the study was inexplicably short. For example, the median survival of women with optimally debulked ovarian cancer treated postoperatively with intraperitoneal chemotherapy was recently reported as 66 months.[38] Additionally, only 46% of the primary debulking operations resulted in an optimal result with less than 1 cm of residual disease. Thus, a more aggressive initial attempt might have led to a better outcome for the group randomized to surgery. It is also interesting to note that the EORTC was the group previously showing a survival

advantage by performing interval debulking, whereas the GOG trial did not show any benefit.

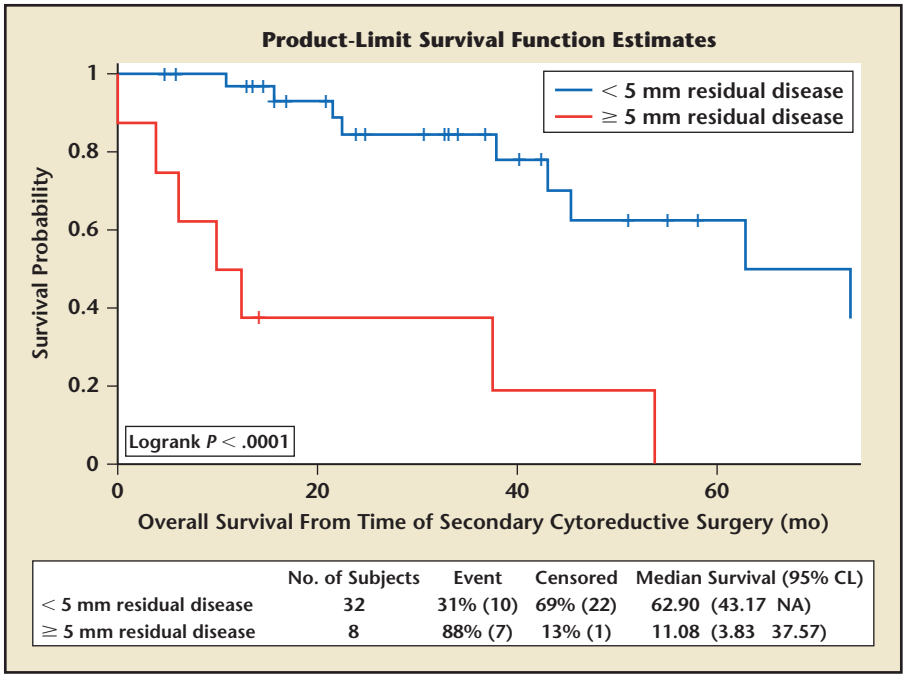
Secondary Debulking Surgery

Although the rationale for a second debulking operation is largely an extrapolation of the reasoning for primary surgery, there are several reasons the certainty of clinical benefit is even more contentious. Recurrent ovarian cancer has a much more heterogeneous disease presentation. As a result, treatment is typically more individualized. Secondary debulking is generally considered to be most effective when there is a single isolated relapse, a long disease-free interval after completion of primary therapy (ie, more than 12 months), when the patient is reasonably healthy, and when resection to minimal or no residual disease can be achieved (Figure 3). In contrast, women with symptomatic ascites, carcinomatosis, early relapse (ie, less than 6 months), and poor conditioning are least likely to benefit.[39-42]

The clinical reality is that most patients will fall somewhere between these clinical extremes. Chi and colleagues[43] proposed guidelines that are generally accepted, but in practice gynecologic oncologists use their own criteria for determining which, if any, patients are good candidates for secondary surgery. The previously reported retrospective series largely reflects this selection bias. Consequently, the success rates of optimal secondary debulking surgery and the corresponding survival data vary broadly. The potential for significant morbidity and the notable lack of benefit for patients who are left with residual disease emphasize the importance of careful counseling and preoperative assessment of patients.

Two large, prospective, randomized phase III studies are currently underway within the EORTC (protocol 55963) and GOG (protocol 213). Both were designed to assess the value of secondary debulking in the treatment of relapsed ovarian cancer. Unfortunately, it will be years before the results from these trials are finalized. In the meantime, practice patterns will largely continue to be guided by the results of retrospective studies.

Figure 3. *Overall survival of secondary debulking by amount of residual disease. CL, confidence limits; NA, not applicable. Reprinted from* International Journal of Gynecology and Obstetrics, *Vol. 108, Schorge JO et al, "Secondary cytoreproductive surgery for recurrent platinum-sensitive ovarian cancer," pp. 123-127, Copyright 2010, with permission from Elsevier.*[42]



	No. of Subjects	Event	Censored	Median Survival (95% CL)
< 5 mm residual disease	32	31% (10)	69% (22)	62.90 (43.17 NA)
≥ 5 mm residual disease	8	88% (7)	13% (1)	11.08 (3.83 37.57)

Conclusions

A single maximal debulking attempt does make a clinically important difference in patients with newly diagnosed, advanced ovarian cancer. In the past, primary surgery was usually the treatment of choice based on the preponderance of retrospective data. This remains valid today, especially when radical procedures are used to achieve high rates (75%-80%) of minimal or no residual disease.[44] NACT with interval debulking is another option for patients likely to be unresectable and for those who are not medically suitable to undergo primary surgery due to extent of disease or medical comorbidities.[45] At present, there is still no compelling evidence that NACT prior to debulking surgery is a superior strategy.[46]

Secondary debulking surgery is a clinically beneficial treatment option for selected patients with recurrent platinum-sensitive ovarian cancer. Younger women in good health with a lengthy disease-free interval and isolated tumors are the best candidates for surgery. However, because of the wide spectrum of relapsed disease patterns, proportionally few women undergo a second debulking operation. As of the January 2010 semiannual GOG meeting, fewer than 20% of platinum-sensitive recurrent ovarian cancer patients enrolled in GOG protocol 213 had been enrolled into the surgical treatment arm. Further tertiary, or even quaternary, debulking procedures may be reasonable to consider for highly selected patients in some circumstances.[47,48]

The emerging era of personalized medicine is likely to have a dramatic impact on the management of advanced ovarian cancer. Inherently, it makes little sense to treat all patients diagnosed with this genetically heterogeneous disease using a single approach. In the future, pretreatment molecular profiling may be able to identify subsets of patients most likely to benefit from primary debulking.[49] It is hoped that future trials will resolve the important question of how to triage patients to the appropriate sequence of surgery and chemotherapy. ■

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Main Points

- All patients with ovarian cancer should have a consultation with a gynecologic oncologist to help guide decision making.
- Patients with newly diagnosed, advanced ovarian cancer should have a single maximal surgical debulking effort to achieve minimal residual disease.
- Primary debulking surgery does make a clinically important difference and is the treatment of choice in specialized centers with a high success rate of achieving an optimal result.
- Neoadjuvant chemotherapy with interval debulking surgery is a good option for those patients not initially medically suitable due to extent of disease or medical comorbidities.
- Secondary debulking surgery may be beneficial for the relatively few patients who have an isolated relapse after a lengthy disease-free interval.

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